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09/763,836	06/08/2001	Osamu Yamada	19036/37156	3756

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EXAMINER	
PAPPU, SITA S	
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1636	

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Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No. 09/763,836	Applicant(s) YAMADA ET AL.	
	Examiner Sita Pappu	Art Unit 1636	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *01 February 1102* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-6,8-18 and 20-46* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-6,8-18 and 20-46* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☒ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☒ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

Group I and Group III are rejoined. The method of Group II, claim 30, is similar to the method of claim 32 and is, therefore, rejoined with Group I.

Claims 1-6, 8-18, 20-46 are being examined, herein, on their merits.

Priority

An application in which the benefits of an earlier application are desired must contain a specific reference to the prior application(s) in the first sentence of the specification.

Receipt is acknowledged of papers submitted under 35 U.S.C. 119(a)-(d), which papers have been placed of record in the file.

Drawings

Draftsperson objected to the drawings. See attached PTO-948.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 30, 32, 35, 36 and 46 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

While the specification is enabling for a polynucleotide as set forth in SeqID NO:1 and/or SeqID No:7, no pharmaceutical property is shown and/or enabled by the specification for the reasons discussed herein below. Further, claims 30 and 32 encompass in vivo applications and thus, gene therapy. Thus the specification does not enable one skilled in the art to make and use the claimed invention.

There are many factors to be considered when determining whether there is sufficient evidence to support a determination that a disclosure does not satisfy the enablement requirement and whether any necessary experimentation is "undue." These factors include, but are not limited to: (a) the breadth of the claims; (b) the nature of the invention; (c) the state of the prior art; (d) the relative skill of those in the art; (e) the level of predictability in the art; (f) the amount of direction provided by the inventor; (g) the existence of working examples; and (h) whether the quantity of experimentation needed to make or use the invention based on the content of the disclosure is "undue" (MPEP 2164.01 (a)).

Nature of the Invention:

Claims 30, 32, 35, 36 and 46 are drawn to method of expressing and/or enhancing the expression of a polynucleotide and therapeutic compositions and use of the compositions in gene therapy for the treatment of diseases resulting from reduction of cap-dependent mRNA translation and/or resulting from reduction of IRES activity in a body of organisms.

Breadth of claims:

Claims 30, 32, 35, 36 and 46 encompass the expression and use of the nucleic acid sequences in the treatment of any and all diseases resulting from reduction of cap-dependent mRNA translation and/or resulting from reduction of IRES activity in a body of organisms and gene therapy and include any and all organisms and are, therefore, very broad.

Amount of guidance in the specification and working examples:

The specification does not disclose the use of these polynucleotides in gene therapy. Nor does it disclose the use of these polynucleotides in the treatment of any disease(s) in any organism. Thus the specification is not enabling for the use of these nucleic acid sequences in gene therapy and/or for the treatment of any diseases in any organism. The specification discloses that the nucleic acid sequences of the instant invention result in enhancement of expression of genes that are downstream of the nucleic acid sequences of the instant invention and demonstrates the enhanced gene expression in vitro and in cell lines (specification, page 36, lines 4-7 and table 2; page 38, lines 12-19; page 40, table 5; page 41, lines 1-6; figure 10; page 47, lines 11-21). Other than this, the specification does not disclose any pharmaceutical property for this said polynucleotide in the form of a composition. Prophetic examples of how different diseases can be treated with the nucleic acid sequences of the instant invention and how the said sequences can be used in different vectors used in gene therapy are provided (page 51, lines 4-6 and 14-16). These examples in the specification do not disclose the phenotype or behavior of the said organism after administering the vectors containing these sequences and/or the effect of such vectors in exhibiting a therapeutic

effect or the mode of using the said polynuelotide in treating any disease in any organism. In the absence of specific guidance, one of skill in the art would be required to engage in undue experimentation to make and use the invention as claimed.

State of the art, skill level of the artisan, predictability of the invention and amount of experimentation necessary:

Even though the skill of an artisan in this subject area is considered to be very high, it would require undue experimentation on the part of an artisan to make and use the claims as specified and use the invention as claimed. The specification and the working examples do not provide sufficient guidance to practice the invention as claimed.

At the time of filing, gene therapy utilizing the direct administration of recombinant nucleic acids, whether in the form of retroviruses, adenoviruses, or plasmid DNA/liposome complexes, was considered to be highly unpredictable. Verma et al. states that, "[t]he Achilles heel of gene therapy is gene delivery..", and that, "most of the approaches suffer from poor efficiency of delivery and transient expression of the gene" (Verma et al. (1997) Nature, Vol. 389, page 239, column 3, paragraph 2). Marshall concurs, stating that, " difficulties in getting genes transferred efficiently to target cells- and getting them expressed- remain a nagging problem for the entire field", and that, "many problems must be solved before gene therapy will be useful for more than the rare application" (Marshall (1995) Science, Vol. 269, page 1054, column 3, paragraph 2, and page 1055, column 1). Orkin et al. further states in a report to the NIH that, " .. none of the available vector systems is entirely satisfactory, and many of the perceived

advantages of vector systems have not been experimentally validated", and that," [w]hile the expectations and the promise of gene therapy are great, clinical efficacy has not been definitively demonstrated at this time in any gene therapy protocol" (Orkin et al. (1995) "Report and recommendations of the panel to assess the NIH investment in research on gene therapy", page 1, paragraph 3, and page 8, paragraph 2). Among the many factors that the art teaches affect efficient gene delivery and sustained gene expression are anti-viral immune responses, particularly against adenoviral proteins, and the identity of the promoter used to drive gene expression. Verma et al. teaches that weak promoters produce only low levels of protein, and that only by using appropriate enhancer-promoter combinations can sustained levels of therapeutically effective protein expression be achieved (Verma et al., *supra*, page 240, column 2). Verma et al. further warns that, " .. the search for such combinations is a case of trial and error for a given type of cell" (Verma et al., *supra*, page 240, bridging sentence of columns 2-3). Thus, the art at the time of filing clearly establishes that expectation for achieving a desired therapeutic effect *in vivo* by expressing a therapeutic gene using any of the expression constructs known in the art at the time of filing was extremely low.

Thus, due to the art recognized unpredictability of achieving therapeutic levels of gene expression following direct or indirect administration of nucleic acid vectors, the lack of guidance provided by the specification for the parameters affecting delivery and expression of therapeutic amounts of DNA into the cells, the lack of guidance concerning the treatment of any and all diseases in any and all organisms using the polynucleotide sequences of the instant invention, it would have required undue

experimentation to practice the instant invention and the skilled artisan would not have predicted success in treating the wide variety of diseases as claimed.

Claims 37 and 43 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

Nature of the invention in case of claims 37 and 43 is directed toward a method of detecting the presence of HCV 5' UTR variant as set forth in SeqID NO.7 in a biological sample from a test subject and determining the severity of HCV infection based on the presence of this sequence in the said sample.

Breadth of claims: Claims 37 and 43 encompass determining the severity of HCV infection in any and all subjects and by detecting the presence of any and all variants of HCV 5' UTR using the nucleic acid sequence of SeqID No. 7, and are extremely broad.

The amount of guidance in the specification and working examples are insufficient to support the breadth of the claims. The specification discloses the nucleic acid sequence of HCV 5' UTR in SeqID No. 1 and a variant of this sequence in SeqID No. 7. Other than these two sequences, the specification does not describe all the known variants of HCV 5' UTR. Nor does it disclose what other variants are possible in the HCV 5' UTR sequence and how all these variant forms of 5' UTR sequences contribute to the severity of HCV infection. The specification discloses that the patient from whom the HCV 1b strain and the resulting nucleic acid sequence of SeqID NO. 7

was derived (specification, page 41, example 7) suffered from hyperviremia and it was postulated that it could be due to high viral replication. The specification on page 44, lines 23-25 speculates that the 4x higher luciferase gene expression when this sequence was used as IRES could be due to the insertion of a thymidine at position 207 of SeqID No.1 resulting in SeqID No.7, and that characteristics of the infected HCV can be identified by specifically detecting HCV 5' UTR sequences having a thymidine inserted at position 207 (page 48, lines 24-28). The only other guidance provided in the specification that pertains to the method of determining the severity of HCV infection in a test subject is on page 51, lines 17-19, where it was disclosed that the sequence of SeqID NO. 7 could be used to determine the severity of hepatitis C through detecting the presence of an HCV-derived specific polynucleotide sequence contained in a biological sample derived from a test subject. Other than this, no other specific guidance was provided such that a skilled artisan would accept that the sequence of SeqID NO. 7 would be sufficient to determine the severity of infection due to any and all HCV strains in any and all test subjects.

State of the art, Skill level of the artisan, predictability of the invention and amount of experimentation necessary:

Prior art teaches the sequence of the 5' untranslated region of hepatitis C virus and identifies the similarities between the HCV UTR sequence and those of other picornaviruses. Borman et al. (1995) state that while all the picornaviral UTRs can direct internal ribosome entry, the functional requirements for efficient IRES activity can vary dramatically (page 3656, left column, lines 23-25) and that HCV shows specific affinity

for proteins present in extracts from BSC-related cell lines (page 3662, left column, bottom paragraph, lines 4-8). In such a situation, the efficiency and the corresponding level of enhancement exhibited by SeqID No. 7 or any other HCV UTR may vary depending on the variability in the functional requirements available and thus, the association of the presence a particular sequence with a certain level of severity of HCV infection becomes an unpredictable issue.

Further, Laporte et al. (2000, Journal of Virology, vol. 74, no.22, pp. 10827-10833) state that HCV has a very high mutation rate and circulates as a population of closely related genomes, referred to as quasispecies (page 10827, left column, paragraph 2, lines 6-9). Thus, the association between the SeqID No.7 which is just one variant of SeqID No. 1 of HCV1b and hyperviremia is always not definitive and the hyperviremia exhibited by the patient carrying the SeqID no. 7 could be due to any other variant present in the patient's system. Thus, it is unpredictable how one of skill can associate a particular sequence of HCV UTR with a particular level of severity. Considering that many mutant forms and/or populations of sequences may be present in any one test subject, determining the presence of each and every one of these forms in the test subjects and then trying to associate these sequences with the severity of the disease becomes an arduous and unpredictable task for even one with a relatively high level of skill in the art. Since the prior art does not teach which mutation results in what type and level of hyperviremia and/or severity of hepatitis, for the claims to be enabled the specification must teach all the possible mutations and associated severity levels of infection such that a skilled artisan can practice the invention without undue

experimentation. In view of lack of guidance regarding the types of mutations and the associated severity of infection, it would require undue experimentation on the part of a skilled artisan to practice the invention as claimed. Thus, the claims 37 and 43 are not enabled by the specification over any scope.

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 1-6, 8-18, 20-25, 38-40, 44, 45 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 1-6, 8-18, 20-25, 38-40, 44, 45 are indefinite in their recitation of "a nucleic acid sequence" which is just a collection of A, C, G, Ts in a certain order and could possibly be the subject of a copyright. A nucleic acid sequence is not a composition. Use of claim language such as "an isolated polynucleotide comprising a nucleic acid sequence for..." is suggested.

Claims 14, 15, 17, 18, 20, 22, 26, 32, 33, 38, 39, 40, 41 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 14, 15 are indefinite in their recitation of "according to claim 12 " and claims 17, 18 are indefinite in their recitation of "according to claim 13 " and claims 20 and 22 are indefinite in their recitation of "according to claim 1". It is not clear whether

this phrase is referring to the method of "enhancing expression of a useful gene" or to "the nucleic acid sequence". Clarification is required.

Claim 26 is indefinite in its recitation of "nucleotide sequence of SeqID NO:7". Use of claim language such as "nucleotide sequence as set forth in SeqID NO:7" is suggested.

Claim 26 is indefinite in its recitation of "a nucleotide sequence of SeqID NO:7". This encompasses any fragment of SeqID NO:7. Use of claim language such as "consisting of the nucleotide sequence as set forth in SeqID NO: 7, over its entire length" is suggested.

Claim 32 is indefinite in its recitation of "using the vector according to claim 28". It is unclear how the vector would be "used". Method does not include a step whereby gene expression is enhanced. Therefore, the method steps are in conflict with the preamble, because the recited steps do not accomplish what the preamble implies the method steps are intended to accomplish.

Claims 33 and 41 are indefinite in their recitation of "substances". The meaning of this term is not clear. Clarification is required. Alternately, Applicant should point to where in the specification this term is defined.

Claims 38, 39 and 40 are indefinite in their recitation of "having one thymidine inserted into position 207 of SeqID No:1". Claims 38-40 depend from claim 21, which already recites the insertion of thymidine into position 207. Therefore, it is not clear if the thymidine insertion recited in claims 38-40 is an additional insertion. Claims 38-40, in the present form, are confusing. Clarification is required.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 1-6, 8-13, 16, 21, 22, 28, 29, 31, 32, 35, 44, 45, are rejected under 35 U.S.C. 102(b) as being anticipated by Yoo et al. (1992, Virology, vol. 191, pp. 889-899).

Yoo et al. (1992) teach a vector comprising a nucleic acid sequence of the 5' UTR of hepatitis C virus (page 890, left column, bottom paragraph and page 891, right column, bottom paragraph) enhancing the expression of CAT protein in vitro and CAT enzymatic activity in vivo in mammalian cells (page 892, left column, lines 1-2).

In particular, they teach that the nucleotides 1-341 of the 5' UTR were introduced into the vector (page 891, right column, bottom paragraph) and several deletion constructs (Fig. 1 C) were used in studying the expression-enhancing ability of HCV 5'UTR. The presence of a pyrimidine tract (page 896, right column, line 1), a trans factor binding site or a ribosome landing pad (page 897, left column, line 8), and AUG or ATG within the ORFs, and an IRES in the 5' UTR of HCV are all inherent features to the 5' untranslated region of HCV. The vector taught by Yoo et al. (1992) is a vector for expression in mammalian cells (Figure 3 and page 890, left column, subsection 'cells, bacterial strains and plasmids). Further, HCV is an RNA virus (page 889, left column, line 3-5). The nucleic acid sequence of the 5' UTR of HCV is an inherent feature of the

HCV 5' UTR and by teaching the 5' UTR, Yoo et al. (1992) anticipated the sequence of the 5' UTR of HCV. Further, the limitations of claim 21 are anticipated by Yoo et al. (1992) because claim 21 encompasses a nucleic acid sequence comprising the nucleotides 181-341 of SeqID NO:1, or a fragment or variant thereof.

Yoo et al. (1992) further teach the poliovirus (a picornavirus) 5' UTR sequence in one of the expression vectors (page 890, right column, line 19).

For claim 35, even though the polynucleotide is not enabled for its intended use as a composition, the polynucleotide itself is disclosed in the prior art. Since the claim is directed to a composition, the intended use of the claimed composition is given patentable weight when making a determination of patentability under 35 U.S.C. 102 only when it serves to define a structural requirement. In composition claims, intended use must result in a structural difference between the claimed invention and the prior art in order to patentably distinguish the claimed invention from the prior art. Furthermore, the preamble is generally nonlimiting if it merely recites an inherent property. See MPEP 2111.02. In the instant case, the prior art structure has all the features required to perform the intended use recited in the claims. Furthermore, as there are no claimed distinguishing features between the claimed composition and the nucleic acid sequence, the nucleic acid sequence is an inherent feature of the therapeutic composition. The claiming of a new use, new function, or unknown property which is inherently present in the prior art does not necessarily make the claim patentable. *In re Best* 562 F.2d 1252, 1254, 195 USPQ 430, 433 (CCPA 1977). See also MPEP 2112.

Thus, the claimed composition is disclosed in the prior art.

Thus, by teaching all the limitations, Yoo et al. (1992) anticipated the claims 1-6, 8-13, 16, 21, 22, 28, 29, 31, 32, 35, 44, 45.

Claims 23-25, 27, 41, 42, 46 are rejected under 35 U.S.C. 102(b) as being anticipated by Collier et al. (1998, Journal of General Virology, vol. 79, 2359-2366).

Collier et al (1998) teach a novel bicistronic dual luciferase reporter construct assay system for studying translational efficiencies of 5' UTR from hepatitis C virus, wherein the translation of firefly luciferase is directed by HCV 5' UTR as an IRES in vivo (Figure 2, page 2362 and Figure 3, page 2364) in vivo (paragraph 2, page 2363) and in vitro (page 2364, left column, lines 1-5).

For claim 46, even though the polynucleotide is not enabled for its intended use as a composition, the polynucleotide itself is disclosed in the prior art. Since the claim is directed to a composition, the intended use of the claimed composition is given patentable weight when making a determination of patentability under 35 U.S.C. 102 only when it serves to define a structural requirement. In composition claims, intended use must result in a structural difference between the claimed invention and the prior art in order to patentably distinguish the claimed invention from the prior art. Furthermore, the preamble is generally nonlimiting if it merely recites an inherent property. See MPEP 2111.02. In the instant case, the prior art structure has all the features required to perform the intended use recited in the claims. Furthermore, as there are no claimed distinguishing features between the claimed composition and the nucleic acid sequence, the nucleic acid sequence is an inherent feature of the therapeutic

composition. The claiming of a new use, new function, or unknown property which is inherently present in the prior art does not necessarily make the claim patentable. *In re Best* 562 F.2d 1252, 1254, 195 USPQ 430, 433 (CCPA 1977). See also MPEP 2112.

Thus, the claimed composition is disclosed in the prior art.

Thus, by teaching all the limitations, Collier et al. (1998) anticipated the claims 23-25, 27, 41, 42, 46.

Claims 33 and 34 are rejected under 35 U.S.C. 102(b) as being anticipated by Zhang (1998, GenBank accession Number AB016785 submitted on August 05, 1998).

Zhang (1998) teaches the polynucleotide of SeqID No:7 as part of the sequence of the GenBank accession AB016785. Accession AB016785 is 9538 bases long of which the first 342 bases comprise the 5' UTR (SeqID NO:7) of HCV.

Since the claim is directed to a probe comprising the polynucleotide of SeqID NO:7, the intended use of the claimed probe is given patentable weight when making a determination of patentability under 35 U.S.C. 102 only when it serves to define a structural requirement. The intended use must result in a structural difference between the claimed invention and the prior art in order to patentably distinguish the claimed invention from the prior art. Furthermore, the preamble is generally nonlimiting if it merely recites an inherent property. See MPEP 2111.02. In the instant case, in view of the 'comprising' claim language, the prior art structure has all the features required to perform the intended use recited in the claims. Furthermore, as there are no claimed distinguishing features between the claimed probe and the nucleic acid sequence, the

nucleic acid sequence is an inherent feature of the probe. The claiming of a new use, new function, or unknown property which is inherently present in the prior art does not necessarily make the claim patentable. *In re Best* 562 F.2d 1252, 1254, 195 USPQ 430, 433 (CCPA 1977). See also MPEP 2112.

Thus, the claimed probe is disclosed in the prior art.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 23-25, 27, 41, 42, 46 are rejected under 35 U.S.C. 103(a) as being unpatentable over Brown et al. (1992, Nucleic acids research, vol. 20, no.19, pp. 5041-5045) Dirks et al. (1993, Gene, vol. 128, pp 247-249), further in view of Fukushi et al. (1997, Journal of Virology, vol. 71, No. 2, pp.1662-1666).

Brown et al. (1992) teach the sequence and structure of the 5' nontranslated regions of hepatitis C virus (page 5041, right column, lines 20-27).

Brown et al. Do not teach using the 5' nontranslated region of HCV as an IRES.

Dirks et al. (1993) teach dicistronic vectors utilizing the IRES sequence of poliovirus as the intercistronic region for gene expression in mammalian cells (page 248, Figure 1and bridging paragraph, page 248).

Dirks et al. (1993) do not teach using their method and the vector using the HCV 5' UTR sequence.

Fukushi et al. (1997) teach that the translation strategy used by HCV is similar to that employed by members of the family Picornaviridae (page 1662, left column, paragraph 2, lines 1-2) and that HCV IRES is similar to that of picornaviruses (page 1662, left column paragraph 3, lines 1-2) and thereby provide the motivation to use HCV 5' UTR as an IRES.

Therefore, it would have been obvious to one of ordinary skill in the art to substitute the poliovirus IRES in the vector of Dirks et al. with the HCV 5' UTR IRES and study translational efficiency of HCV IRES in a bicistronic vector, with a reasonable expectation of success because Dirks et al. already successfully demonstrated that using a bicistronic vector is an efficient way to study IRES dependent translation in mammalian cells.

Conclusion

No claims are allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Sita S Pappu whose telephone number is (703) 305-5039. The examiner can normally be reached on Mon-Fri (8:30 AM - 5:00 PM).

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Dr. Remy Yucel can be reached on (703) 305 1998. The fax phone

numbers for the organization where this application or proceeding is assigned are (703) 308 4242 for regular communications.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to Tracey Johnson, whose telephone number is (703) 305-2982.

Anne-Marie Baker

ANNE-MARIE BAKER
PATENT EXAMINER

S. Pappu
April 5, 2002